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14. ABSTRACT

The goal of this project is to evaluate, in a screening context, stereoscopic digital mammography versus standard (non-stereo) digital mammography for earlier detection of breast lesions during screening and for reductions in the rate of patient recall for further work-up. At the end of the fourth year of the project, we have enrolled 585 patients into the clinical trial. Following independent reading of the standard and stereo screening mammograms, 115 patients (19.7%) were recalled for work-up studies of 141 reported findings (60 from standard mammography alone, 45 from stereo mammography alone, and 36 reported by both). Work-up examinations confirmed 62 of the reported findings as true positives(including 15 cancers) and 79 as false positives. With regard to true positive findings (detection sensitivity), standard mammography detected 46 and missed 16; stereo mammography detected 49 and missed 13—an improvement in sensitivity of 6.5%. With regard to detection specificity, standard mammography reported 50 false positive lesions while stereo mammography reported only 32—a highly significant reduction of 36% in the rate of false positive detections ($p<.005$). Thus, at this stage of the clinical trial, stereo mammography is demonstrating a modest improvement in sensitivity and a remarkable improvement in specificity relative to standard mammography.

15. SUBJECT TERMS
stereoscopic digital mammography, breast cancer detection, reduced rate of recall, focal abnormality detection

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Table of Contents

INTRODUCTION

The objective of this project is to evaluate stereoscopic digital mammography compared to standard, non-stereo digital mammography in screening for breast cancer. We hypothesize that stereo mammography, by enabling the mammographer to view the internal structure of the breast in depth, will support earlier and more accurate detection of subtle breast lesions and also support more confident dismissal of those it does detect as insignificant and not in need of work-up. We expect, as a consequence, that stereo mammography will perform better than standard mammography with respect both to earlier detection of breast cancer and a reduced rate of recall, and that it will perform with both greater sensitivity and greater specificity in the detection of abnormalities in the breast.

A large part of what we expect to be substantial gains in specificity of stereo over standard mammography will come, we believe, from reduced false positive detections of apparent lesions—chance superimpositions of normal tissue that in the standard mammogram resemble a volumetric focal abnormality. In the stereo mammogram, the otherwise superimposed tissue is seen as separated in depth. With stereo mammography, fewer patients, many fewer we expect, will need to be recalled for further work-up of what would turn out to be such a false positive.

By the end of the project in two years, close to 2000 women who are at elevated risk for development of breast cancer because of personal or family history, will be enrolled in the project and given both standard (non-stereo) and stereoscopic digital mammography screening examinations. The standard and stereo mammographic images will be interpreted in independent readings by different mammographers. The reading data will be analyzed to determine the comparative rates of true lesion detection, and of appropriate recall for further work-up.

Interim results to date are very exciting. With 585 patients currently enrolled in the clinical trial, we are observing a modest improvement in sensitivity (the detection of true lesions) with stereo imaging, and a large and highly significant improvement in specificity (true negatives read as normal), through a large reduction in false positive detections.

BODY OF REPORT

1. Overview of Year 4 Progress

At the end of Year 4 of the project, we have enrolled 585 eligible patients at elevated risk for development of breast cancer into the clinical trial underway at the Emory University Breast Clinic in Atlanta. Each patient received two screening mammograms (a standard digital mammogram and a stereoscopic digital mammogram) which were independently interpreted by different mammographers.

Because of increasing concern early in the project year that the rate of patient accrual into the trial was not adequate, we developed several initiatives to increase public awareness about the clinical trial in the greater Atlanta area. These initiatives included several types of announcements within the Emory Heathcare System and a radio announcement that was aired over several weeks on two radio stations in the Atlanta area. In addition, we have also publicized the trial in several printed and online media. These announcements resulted in an immediate and substantial increase in the number of women enrolling in the clinical trial. We have also been informed that the Army has agreed to our request for a one-year, no-cost extension to the project, thus providing an additional year for patient enrollment.

During this project year, we developed an additional study data form, Form E, to be filled out for each participating patient 12 to 18 months after the initial enrollment and imaging. The purpose of this form is to capture information about any further breast-related imaging, diagnosis or treatment that has occurred to the patient in the intervening months that might affect our understanding of truth for that patient.

We have conducted preliminary analyses of the reading data for the 585 patients enrolled and imaged to date. These analyses include assessment of lesion detection sensitivity and specificity for both standard and stereo mammographic exams. We are very excited by the preliminary results, described in detail below.

2. Patient sample demographics

We began enrolling patients into this study in January, 2005—part way through Year 3 of the project. As of the end of Year 4 (31 July 2006), we have enrolled 585 female patients into the clinical trial, all at the elevated risk for development of breast cancer required by the study protocol. In this sample, 69.9% (408 of 585) have had prior breast cancer. Of these 408 patients, 49.5% (202 of 408) have had a single-breast mastectomy.

The mean patient age is 58.5 years, with a standard deviation of 11.4 years. The youngest patient in the sample is 31 years old, while the oldest is 90 years old. The distribution of ages in the patient sample is shown below in Figure 1.

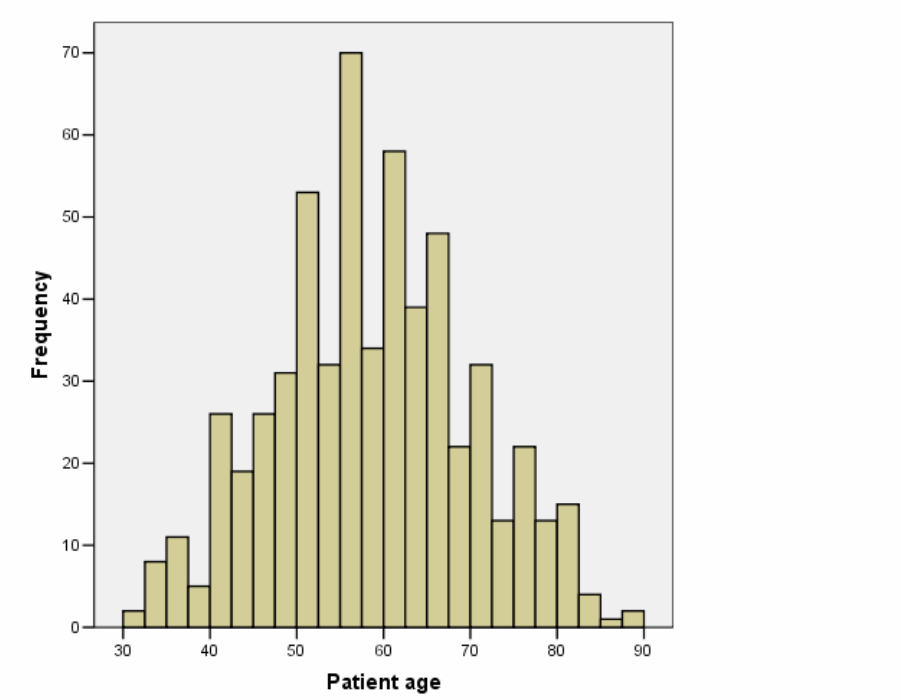

Figure 1. Distribution of patient age in the current patient sample.

Regarding menopausal status, 58.3% (341 of 585) are post-menopausal and 41.7% (244 of 585) are pre-menopausal. And 81.2% of the women (475 of 585) have delivered one or more children, while the remaining 18.8% (110 of 585) have never had children. Of the women who have delivered children, only 14.7% (86 of 475) delivered a first child after age 30.

The distribution of patients by ethnic origin is shown in Table 1 below:

Ethnic Origin	Number of Patients	Percentage
Caucasian	531	90.8%
African American	39	6.7%
Hispanic	9	1.5%
Native American	4	0.7%
Asian, Pacific Islander	1	0.2%
Other	1	0.2%

Table 1. Ethnic origin of patients in the clinical trial

3. Patient recruitment

We show below in Figure 2 both the monthly and cumulative numbers of patients enrolled in the study. By the early months of the current Year 4 of the project—in the fall of 2005—it was becoming clear that the average rate of patient enrollment, about 24 patients per month, was not sufficient to develop a sample of patients approaching 2000 by the end of the project. As a result we undertook several initiatives beginning early in 2006 to increase awareness of the clinical trial in the greater Atlanta area and to encourage eligible women to inquire about participation. These initiatives, described below, have been quite successful in increasing the average rate of patient enrollment, which is now averaging about 47 patients per month. The improvement is visible as an increased slope of the cumulative curve in Figure 2 in 2006 compared to 2005.

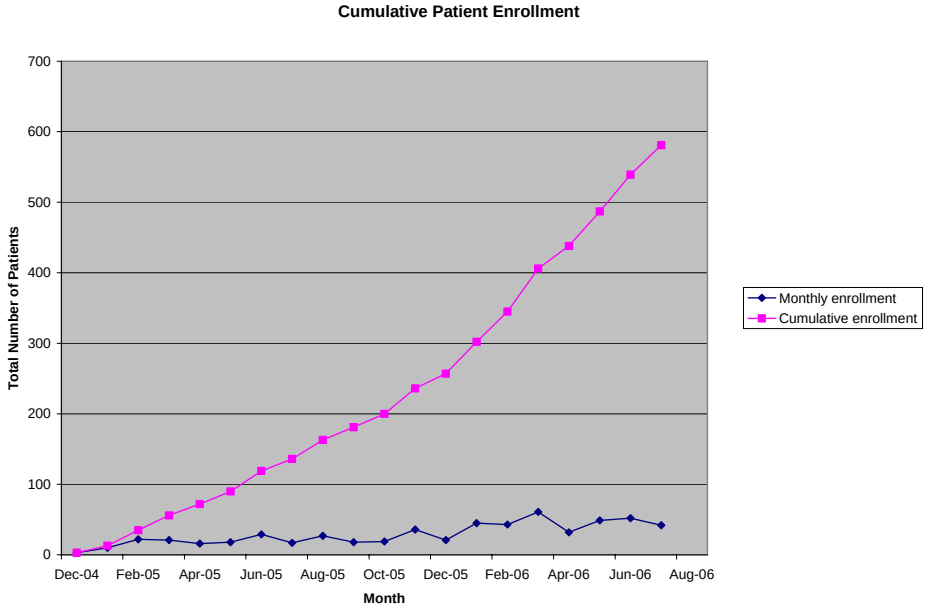

Figure 2. Monthly and cumulative patient enrollment numbers.

Three different approaches were used to increase public awareness. These initiatives required an expenditure of $15K by the Emory Public Relations department. These funds were provided by a formal contract modification approved by the Army, shifting $15K from BBN's research funds to the Emory subcontract.

First, we publicized the clinical trial widely through the Emory Healthcare system. This effort included: (1) leaving stacks of descriptive handout cards at appropriate locations within the hospital system, (2) including a verbal description of the trial in telephone on-hold messages heard by patients calling into the hospital system, and (3) including a notice about the trial on the Emory Healthcare web site:

http://www.emoryhealthcare.org/care_centers/clinicaltrials/clinicaltrials/Stereoscopic_Digital_Mammography_Study.html

Second, we developed a radio announcement that was delivered on 2 radio stations in the Atlanta area between April 24, 2006 and May 19, 2006. The announcement was presented each weekday for a week in the AM and PM drive times, as well as during the day. This was repeated for a second week following a week off.

The 2 radio stations were chosen to address quite different audiences. One station was WABE (90.1 FM) which is a Public Broadcasting System station with a classical music orientation and broadcasts of National Public Radio programs. The second station was WLTM (94.9 FM) which largely plays lighter popular and oldies music. The station is heard as background music in many professional offices around Atlanta.

Third, an announcement of the trial was published in the Atlanta Intown Newspaper in the May and June issues, delivered to well over 17,000 homes in the Buckhead zone of Atlanta. In addition, a web link to the trial continues to be included in the online version of the newspaper:

http://www.atlantaintownpaper.com/

As a further step, we also requested from the Army a one-year, no-cost extension to the project, shifting the end of the project from July 31, 2007 to July 31, 2008. This extension has been approved and will enable 2 more years of patient accrual. If we continue to enroll about 50 patients per month over the remaining 2 years of the project, we can anticipate accruing an additional 1200 patients, for a final sample size of about 1800 patients. Given that we are already observing statistically significant effects of stereo screening with our current sample of about 600 patients, as described below in Section 5 of the report, we feel confident that the final sample size will be adequate to support reliable statistical analyses of the results.

4. Study data form E

During Year 4, we designed one additional study form, "SDM Data Form E – 18-Months Follow-Up Call," included here as Appendix A. This form is used for each patient in the study to document information about any breast-related imaging studies, breast disease, or treatment that a patient has experienced in the period of 12 to 18 months following enrollment in the study. This information is used to confirm or modify the lesion detection truth data established at the time of the original study screening or subsequent work-up examination.

Follow-up contact with most study patients will occur when the patient returns a year later to the Emory Breast Clinic for her annual screening mammogram. Since we first began enrolling patients into the study in January of 2005, we began to see patients returning for their annual screening mammograms early in 2006. For the small number of patients who do not return to the

Emory Breast Clinic for another screening mammogram within 18 months, we then attempt to reach the patient and fill out Form E through a telephone interview.

5. Study results

5.1 Cases with reported findings

Based on the standard mammogram reading alone, the stereo mammogram reading alone, or on both readings, one or more findings were reported in 19.7% (115 of 585) of the cases. The breakdown by reading condition is shown below in Table 2.

Reading Condition	Number of Cases With Reported Findings
Standard alone	55
Stereo alone	39
Standard & Stereo	21
Total	115

Table 2. Number of cases with reported findings by reading condition

Adding up the unique and shared cases with findings for each reading condition, we observe that standard mammography reported findings for 13% (76 of 585) of the cases, while stereo mammography reported findings for only 10.3% (60 of 585). We will see in analyses described below that the higher number of cases with reported findings for standard mammography is due to many more false positive detections.

As shown in Table 3, while most cases with reported findings had only a single finding, there were some cases with more than one reported finding.

Number of findings in case	Number of cases
1	95
2	15
3	4
4	1

Table 3. Distribution of number of findings per case.

As a result, the total number of findings that were subsequently subjected to work-up examinations was 141.

5.2 Sensitivity of lesion detection

We are interested in comparing the sensitivity of lesion detection for standard and stereo mammography, where sensitivity of a reading condition is the proportion of all worked-up findings reported as abnormal by that reading condition that are shown to be true lesions. The power of this analysis is strengthened in this study by the fact that each patient is included in both the standard and stereo reading conditions. Truth for a reported finding is determined by the results of subsequent work-up examinations and, in some cases, biopsy. The work-up examinations may include other specialized mammographic images such as spot compression

views, magnification views, rolled views, ninety-degree lateral views and exaggerated views. Ultrasound examination is frequently used to differentiate solid from fluid-filled masses. In addition, other imaging modalities, such as MRI, may be utilized occasionally.

The results of our sensitivity analysis for standard and stereo mammography are shown below in Figure 3. Of the 141 reported findings subjected to work-up examination, 62 (44%) were shown to be true lesions. As seen in Figure 3, standard mammography reported 46 of the 62 true lesions (74.2%), missing the other 16 lesions (25.8%). Stereo mammography reported 49 of the 62 true lesions (79.0%), missing the other 13 lesions (21.0%). Thus stereo mammography is demonstrating a modest improvement in lesion detection sensitivity (4.8%). The difference is not statistically significant (p>.5).

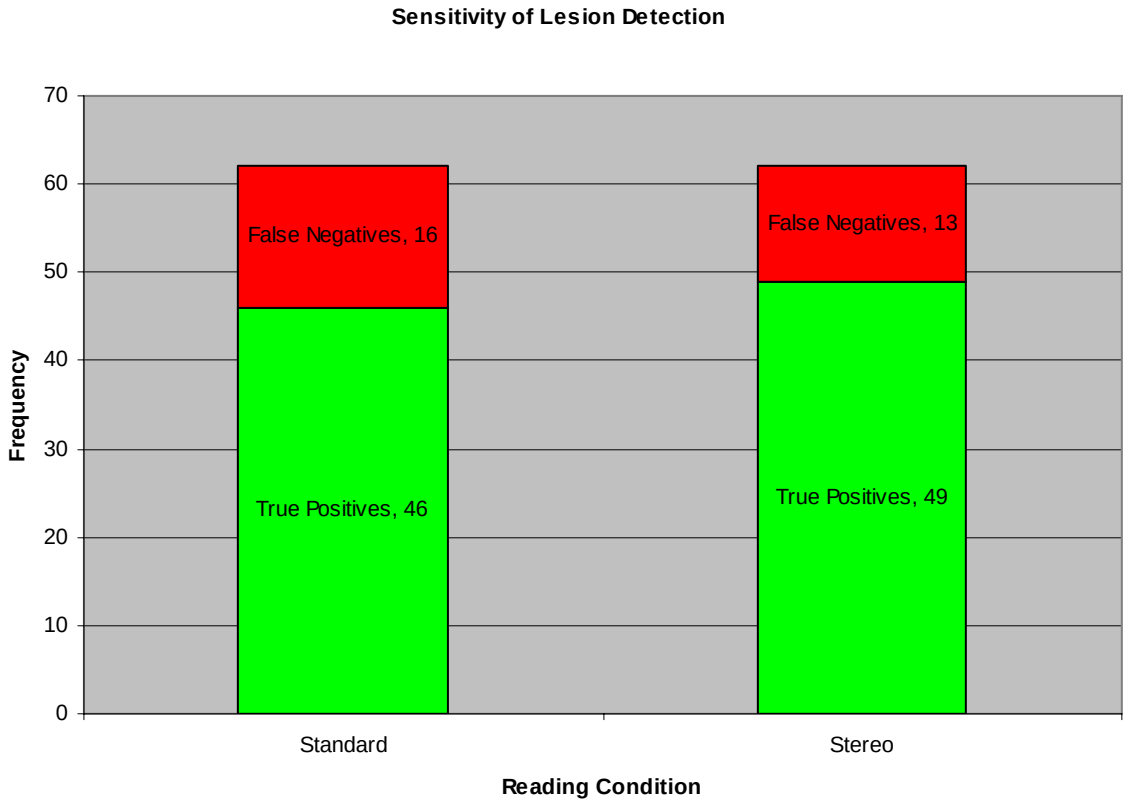

Figure 3. Sensitivity of lesion detection for standard and stereo mammography.

5.3 Specificity of lesion detection

We are also interested in comparing the specificity of lesion detection for standard and stereo mammography. Specificity is the proportion of all worked-up findings reported as normal by a reading condition that are shown at work-up to be normal.

The results of our specificity analysis for standard and stereo mammography are shown below in Figure 4. Of the 141 reported findings identified by standard mammography, stereo mammography, or by both for work-up examination, 79 (56%) were shown to be false positives, with no lesion found. As seen in Figure 4, standard mammography reported 50 of the 79 findings (63.3%) that turned out to be false positives, correctly reporting the other 29 cases (36.7%) as normal. Stereo mammography reported only 32 of the 79 findings (40.5%) that turned out to be false positives, correctly reporting the other 47 cases (59.5%) as normal. Thus stereo mammography is demonstrating a very large reduction in the number of false positive reports (18 fewer false positives), amounting to a 36% reduction in false positives over standard mammography. The difference is highly statistically significant ($p<.005$). This result is of large practical significance as well since it implies that 36% fewer women would be needlessly recalled for work-up examinations, avoiding both the expense and anxiety produced by the recall.

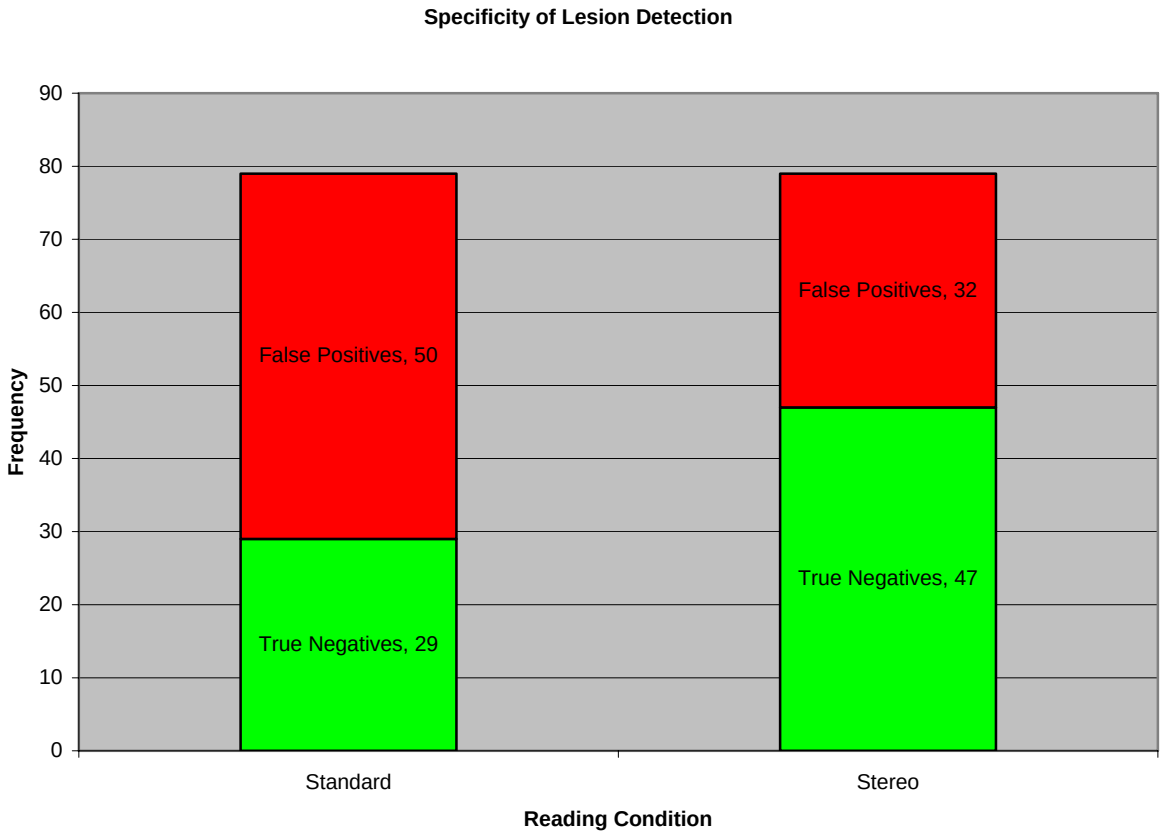

Figure 4. Specificity of lesion detection for standard and stereo mammography.

5.4 Biopsied lesions

Of the 62 true lesions confirmed by work-up examination, 21 were recommended for biopsy. As a result of biopsy, 15 of the lesions were determined to be malignant, while the other 6 were benign.

Standard mammography detected 12 of the 15 malignant lesions (80%), missing the other 3, and detected 5 of the 6 benign lesions, missing 1. Stereo mammography detected 13 of the malignant lesions (87%), missing the other 2, and detected all 6 of the benign lesions. Thus, stereo mammography appears to slightly more sensitive in detecting cancer and worrisome lesions than standard mammography, although the frequencies are too small to support statistical analysis.

KEY RESEARCH ACCOMPLISHMENTS (Year 4)

- Of the 62 reported lesions in the current patient sample which were confirmed to exist by work-up examinations, stereo mammography detected 49 and standard mammography 46, demonstrating a slightly higher detection sensitivity for stereo mammography compared to standard mammography. The difference is too small, at present, to attain statistical significance. Importantly, stereo mammography detected one additional cancer missed by standard mammography.

- Of the 79 reported lesions in the current patient sample determined to be false positive detections by work-up examinations, stereo mammography reported only 32 false positives while standard mammography reported 50, demonstrating a highly statistically significant improvement ($p<.005$) in lesion detection specificity for stereo mammography compared to standard mammography.

REPORTABLE OUTCOMES (Year 4)

PRESENTATIONS

MIPS (Medical Image Perception Society)

Getty DJ, Pickett RM and D'Orsi CJ. Stereoscopic digital mammography. MIPS XI Conference, Lake Windermere, UK, September 27-30, 2005.

RSNA (Radiological Society of North America)

Getty DJ. Stereoscopic and bi-plane imaging. Special Refresher Course presentation at the Annual Meeting of the Radiological Society of North America, Chicago, November 27 - December 2, 2005. This course used the syllabus referenced in Getty DJ (2003).

CONCLUSIONS

By the end of Year 4 of the project, we have now accumulated a sample of nearly 600 patients. During early months of the project year, a slowing rate of patient enrollment raised concerns about our ability to generate an adequately large case sample by the end of the project to support reliable statistical analysis of the data. Consequently we undertook several initiatives to increase public awareness about the clinical trial in the greater Atlanta area. These initiatives included (1) several types of announcements within the Emory Heathcare System, (2) radio announcements that were aired on two radio stations in the Atlanta area, and (3) announcements in several printed and online media in the Atlanta area. These announcements resulted in an immediate and substantial increase in the number of women enrolling in the clinical trial. We had also requested from the Army a one-year, no-cost extension to the project, as a further means of increasing the final patient sample size. We have heard, informally, that this request has been granted.

In recent weeks, we have conducted preliminary analyses of the data collected on the current sample of 585 patients. The principal results concern measures of sensitivity and specificity for stereo mammography compared to standard mammography. We have found that stereo mammography is demonstrating a modest increase in lesion detection sensitivity compared to standard mammography, including finding one additional cancer missed by standard mammography. And we have found that stereo mammography is showing a very highly significant improvement in specificity compared to standard mammography, by dramatically reducing the number of false positive lesion detections. If these results continue to hold with increasing sample size, as we fully expect, they will show that stereo mammography could have a very significant impact on improving screening mammography in the future.

REFERENCES

Getty, D. J. Stereoscopic and biplane digital radiography. In E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography*. RSNA Publications, 2003; 199-209.

APPENDICES

- Appendix A: SDM Study Data Form E: 18-Months Follow-Up Call

SDM DATA FORM E – 18-MONTHS FOLLOW-UP CALL

PATIENT STUDY NUMBER:

DATE STUDY DONE:

DATE OF CALL:

CALLER'S INITIALS:

1. Other imaging studies since study digital mammogram?

Ultrasound	Yes	(R L)	No
Mammogram	Yes	(R L)	No
MRI	Yes	(R L)	No
Other	Yes	(R L)	No

2. If Yes, recommendation resulting from the exam(s):

Normal screening
Accelerated follow-up
Biopsy

3. Breast biopsy since study digital mammogram? Yes (date) _____ No

If Yes, continue:

4. Type of Biopsy: Excision Percutaneous
5. Side of Biopsy: Right Left Bilateral
6. Results of Biopsy: Left: Benign Malignant
   Right: Benign Malignant
7. **If malignant, treatment:** Lumpectomy/Radiation Therapy
   Mastectomy
   Lumpectomy only
   Chemotherapy